Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Prolonged Fever and Coronary Artery Involvements: Kawasaki Disease or Systemic Juvenile Idiopathic Arthritis?

Mehrnaz Olfat (MD)[1], Rahele Assari (MD)[1,2,3], Mohamad-Taghi Majnoon (MD)[1,2], Vahid Ziaee (MD)[2,3,4*]

[1] *Children's Medical Center, Pediatric Center of Excellence, Tehran, Iran*
[2] *Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Pediatric Rheumatology Iranian Society, Tehran, Iran*
[4] *Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran*

ARTICLE INFO

Article type
Case Report

Article history
Received: 13 February 2023
Revised: 19 September 2023
Accepted: 08 October 2023

Keywords
Coronary artery
Ferritin
Kawasaki disease
Systemic onset juvenile idiopathic arthritis

ABSTRACT

Introduction: The symptoms and laboratory findings of Kawasaki disease (KD) and systemic-onset juvenile idiopathic arthritis (SoJIA) may overlap in the early phases. Coronary artery lesions are common complications seen in KD.

Cases Presentation: In this article, we report three cases of SoJIA (two males and one female) with prolonged relapsing fever and coronary artery involvement. Initially, all three cases were presumed to have KD and were treated with IVIG. All three cases had arthritis and lymphadenopathy, and one of them had a skin rash. After 3-8 weeks, fever and main clinical symptoms returned. In the second evaluation, they met the criteria for SoJIA and were treated with methylprednisolone, ibuprofen, and methotrexate. High ferritin levels were observed in all three cases (mean=6024 ng/ml).

Conclusion: Coronary artery involvement may rarely be seen in the early phases of SoJIA. Continuing or relapsing fever, late-onset arthritis, and increased serum ferritin levels may help distinguish SoJIA from KD.

Please cite this paper as:
Olfat M, Assari R, Majnoon MT, Ziaee V. Prolonged Fever and Coronary Artery Involvements: Kawasaki Disease or Systemic Juvenile Idiopathic Arthritis?. Rev Clin Med. 2023;10(3): 25-29

Introduction

Kawasaki disease (KD) and systemic-onset juvenile idiopathic arthritis (SoJIA) are two febrile inflammatory illnesses in children that exhibit similar clinical and laboratory manifestations in the early phase of the disease, such as prolonged fever, lymphadenopathy, rashes, arthritis, and increased inflammatory markers (1). However, the presence of splenomegaly, generalized lymphadenopathy, and frequent febrile episodes may suggest SoJIA over KD, making the definitive diagnosis challenging at times (2). Although coronary artery lesions are a known complication of KD, they are rarely reported in patients with SoJIA (3).

Prolonged fever, along with increased inflammatory markers and coronary artery involvement, is usually diagnosed as incomplete KD and treated with intravenous immunoglobulin (IVIG). However, patients with KD who are IVIG-resistant will eventually improve with methylprednisolone, which is an effective treatment for SoJIA. Moreover, early administration of methylprednisolone pulses could prevent macrophage activation syndrome (MAS), a life-threatening complication of rheumatologic and inflammatory disease that is much less frequent in KD than in SoJIA (4). Transient response to IVIG and recurrent episodes of fever favor a diagnosis of SoJIA (1, 2, 5, 6). Some manuscripts have

***Corresponding author:** Vahid Ziaee,*
Division of Pediatric Rheumatology, Children's Medical Center, No. 62 Dr. Gharib St., Keshavarz Blvd, Tehran 14194, IR Iran.
E-mail: *Ziaee@tums.ac.ir*

also described a combined diagnosis of KD and SoJIA, which is not relevant to our study (7). In this manuscript, we report three cases of SoJIA that were initially diagnosed as KD.

Case Presentation

Clinical, laboratory, and echocardiographic findings of the patients are summarized in Table 1.

Case 1

A four-year-old boy presented to our rheumatology clinic with a high-grade fever for seven days and an ill appearance, followed by generalized maculopapular rashes, right-sided cervical lymphadenopathy, arthralgia, and left knee arthritis. His medical history revealed that he had a short period of isolated and self-limited fever four months ago. The initial evaluation revealed a normal blood leukocyte count, anemia (Hb=8.6 g/dl), thrombocytosis (PLT=426×109/L), elevated ESR (115 mm/hour), and CRP (55 mg/L) levels, normal urine analysis, normal AST, ALT, and Alb levels. Septic arthritis with normal left knee arthrocentesis was excluded. More specific tests such as parvovirus B19 IgM, anti CCP, PANCA, CANCA, anti dsDNA, ANA, anti ASO titer, and brucellosis tests were also within the normal limits. Ferritin level was 9948 ng/ml. Left main coronary artery (LMCA) ectasia and an abnormal tapering of the right and left coronary arteries (RCA and LCA) were found in the echocardiography test.

He was treated with 2 g/kg IVIG and high-dose aspirin (ASA) with the diagnosis of incomplete KD. The fever and other complaints were resolved two to three days after initiation of therapy, except for left knee arthritis. He was discharged with low-dose ASA. In the first outpatient follow-up (one month after discharge), reduced LMCA size was found. However, he still had knee swelling and no finger desquamation. In the second follow-up (three months after discharge), the LMCA ectasia was improved and RCA was normal, but the arthralgia had progressed with mild swelling in the other joints, including wrists, elbows, knees, and ankles. Elevated ESR and CRP levels (93 and 96, respectively) were also found. So, the diagnosis of SoJIA with coronary artery involvement was raised, and the patient received IV methylprednisolone. The treatment was followed by oral prednisolone (1 mg/kg/day), ibuprofen (30 mg/kg/day), and methotrexate (MTX) (10 mg/m2/weekly). Systemic symptoms were controlled one month after initiation of treatment, and the arthralgia and arthritis subsided after six months. After three months, prednisolone was tapered off, and ibuprofen and methotrexate were continued for the next six months and then gradually tapered off. He was symptoms-free in three years of follow-up.

Case 2

A three-year-old girl was referred to us with fever and arthritis in her knees and right wrist for a week, which led to limping. One month ago, she was admitted to another pediatric hospital due to an isolated prolonged fever (20 days). She was diagnosed with incomplete KD because of fever, increased ESR and CRP levels, and severe brightness of coronary arteries on the echocardiography examination and had received a standard treatment protocol for KD, including IVIG and ASA. In the current admission, we found elevated ESR and CRP levels (71 and 148,

Table 1. Comparison of the clinical manifestations, laboratory, and echocardiographic findings of the patients

	Case 1	Case 2	Case 3
Gender	Male	Female	Male
Age	4	3	8
Fever duration in the current attack, days	7	7	10
Conjunctivitis	No	No	No
Skin rash	Yes	No	No
Arthritis	Yes	Yes	Yes
Lymphadenopathy	Yes	No	Yes
WBC, ×10³/ µl	7.5	12.5	18.2
Hemoglobin, g/dl	8.6	7.9	11.3
Platelet, ×10³/ µl	426	647	560
ESR, mm/h	115	93	85
CRP, mg/l	55	96	65
Ferritin, ng/ml	9948	5626	2500
Echocardiography findings	LMCA ectasia, RCA, and LCA abnormalities	LMCA aneurysm	LAD ectasia, pericardial effusion

respectively), mild leukocytosis (WBC=12500 with 65% PMNs), anemia (Hb=7.9 mg/dl), and thrombocytosis (647×100). Other laboratory data were within normal ranges, including Wright, 2ME, ANA, RF, anti CCP, AST, ALT, and Alb. Ferritin level was 5626 ng/ml. In the ultrasonography, prominent effusion and synovial thickening of the left knee and mild effusion of the right knee and right wrist were reported. The tri-phasic bone scan showed polyarthritis in the knees, left elbow, right wrist, and right hip. In the echocardiography test, an aneurysm in LMCA (5mm) was revealed. Therefore, the diagnosis of SoJIA presenting with an unusual pattern was made. Prednisolone, MTX, and low-dose aspirin were administered. The signs and symptoms improved after a few weeks. In the follow-up visits, the LMCA size was reduced to 3 mm and then normalized completely. The maintenance treatments were tapered off based on standard protocols. However, in long-term follow-up, she had a disease flare-up after one year.

Case 3

The last case involved an 8-year-old boy who presented with a 10-day fever, knee arthritis, and submandibular lymphadenopathy. The symptoms had started three months ago with prolonged fever, generalized lymphadenopathies, and arthritis. He was admitted to a tertiary pediatric hospital and underwent a diagnostic work-up. He had increased ESR and CRP levels and thrombocytosis along with cardiac involvement, mild LAD dilation, and mild pericardial effusion. He was treated with IVIG, a pulse dose of methylprednisolone, and ASA with a diagnosis of KD. The symptoms subsided until the fever started again 10 days ago. In the current admission, the laboratory findings revealed leukocytosis and neutrophilia (WBC=18200, PMN: 72%), thrombocytosis (PLT=560×109/L), elevated ESR (85 mm/hour) and CRP (65 mg/L) levels, and serum ferritin equal to 2500 ng/ml. The bone marrow aspiration and biopsy were normal. The diagnosis of SoJIA was made as a diagnosis of exclusion. The signs and symptoms were resolved after three pulses of methylprednisolone. He was discharged with a maintenance dose of prednisolone and ibuprofen. In the follow-up visits, the complaints improved, but he had two disease flare-ups in the three-year follow-up.

Discussion

The diagnosis of KD and SoJIA is typically based on clinical and laboratory criteria, the clinical suspicion of the clinician, and the exclusion of similar diseases; there are no specific diagnostic tests. Table 2 compares the clinical manifestation, laboratory, and echocardiographic findings of Kawasaki Disease, SoJIA, and MAS.

Fever is a main characteristic in both diseases that tend to be acute self-limiting in KD and chronic relapsing in SoJIA (7). In Dong et al.'s study, the incidence of presumed patients with KD with a subsequent diagnosis of SoJIA was estimated at 0.2%. They were predominantly caucasian and experienced more MAS compared

Table 2. *Comparing clinical manifestation, laboratory and echocardiographic findings of Kawasaki Disease, SoJIA *, and MAS***

		Kawasaki Disease	SoJIA	MAS
Clinical Manifestation	Fever	Almost/ Always	Almost/ Always	Almost/ Always
	Skin Rash	Common (Morbilliform)	Common (Salmon rash)	Uncommon
	Conjunctivitis	Common	Rare	Rare
	Changes in extremities	Common	Rare	Rare
	Lymphadenopathy	Cervical	Generalized	Generalized
	Visceral involvement	Rare	Common	Common
	Arthritis	Uncommon	Always	Common
	Serositis	Rare	Common	Common
	Koebner phenomenon	Rare	Common	Common
Laboratory findings	WBC	↑	↑	↓
	Platelet	↑	↑	↓
	Hb	↓	↓	↓
	ESR	↑	↑	↓
	CRP	↑	↑	↑
	Ferritin	↔↑	↔↑	↑↑
	Liver enzymes	↔↑	↔↑	↑↑
	Triglyceride	↔↑	↔↑	↑↑
Cardiac involvement	Myocarditis	Uncommon	Uncommon	Common
	Pericarditis	Uncommon	Common	Common
	Coronary artery abnormalities	Common	Rare	Rare

*Systemic onset juvenile idiopathic arthritis
** Macrophage activating syndrome

to patients with KD (1). So, when fever relapses, SoJIA should be considered, as well as MAS (4).

Mucous membrane involvement, especially conjunctival injection, is a frequent manifestation of KD, vasculitis of medium and small size vessels. Oxidative stress, endothelial dysfunction, and neutrophil infiltration in the wall of the small vessels in the early phase of KD lead to these mucocutaneous manifestations (8, 9). Conjunctivitis was reported infrequently in KD patients with a subsequent diagnosis of SoJIA (1), which is in line with our study.

Arthritis is present in both diseases. In KD, arthritis is divided into two categories: early-onset polyarticular arthritis in the acute phase and late-onset oligoarticular arthritis in the sub-acute phase. The inflammatory markers in KD with early-onset arthritis are significantly higher compared to KD without arthritis. In pre-IVIG literature, cardiac outcomes such as coronary artery aneurysms and early-onset arthritis were more frequent (1). In the acute phase of KD, the arthritis is symptomatic and painful with notable inflammatory reactions in synovial fluid and most likely will be resolved after IVIG administration. Otherwise, it will be resolved spontaneously 2-4 weeks later in the sub-acute phase (6). In the subacute phase of KD with oligoarticular arthritis, there is more inflammation in the tissues compared to in the systemic circulation (10, 11). Therefore, late-onset arthritis especially unresponsive to IVIG, even in the presence of coronary artery involvement, favors SoJIA over KD. The innate immune system has a critical role in the acute phase of KD. Activated monocytes secrete IL1, IL6, and TNFα, and macrophages cause the acute phase manifestations of KD (12). The number of monocytes/macrophages and the level of IL1, IL6, and TNFα are directly related to coronary artery involvement in KD. In patients with KD and coronary artery involvement non-respond to IVIG, the level of IL10, IL6, INF-y, and TNFα was demonstrated to be higher than the other cytokines (12, 13). IL1 and IL6 are two important cytokines in the pathogenesis of SoJIA, and IL6 also has a critical role in the pathogenesis of vasculitis. Therefore, the pathogenesis of coronary artery involvement in SoJIA and the acute phase of KD may be the same. Observed benefits from the IL-1 receptor antagonist anakinra in both relapsing KD and SoJIA support this finding (1, 14, 15).

In the sub-acute phase of KD, the elastin degeneration of coronary walls progresses to the aneurysm due to vascular inflammation, activation of the acquired immune system, and lymphocytic infiltration. TNFα and its receptor have been shown to be at the highest levels in IVIG-resistant patients with coronary artery aneurysms. Indeed, the polymorphism of TNFα has been demonstrated in this group (16). The genetic variations and super-antigen specifications may play a critical role in this phenomenon.

Inflammation and increased cytokines stimulate macrophages and result in elevated ferritin levels. In SoJIA and KD, especially in IVIG-resistance cases and high TNFα, ferritin levels could be elevated (16, 17). In SoJIA, the innate immune system, macrophages, and cytokines have a more pivotal role in the pathogenesis of the disease than KD (1, 17). In Mizuta et al.'s study, measurement of serum ferritin levels has been suggested as a useful diagnostic marker to differentiate SoJIA from KD, as higher ferritin levels favor the diagnosis of SoJIA (17). Our three cases also showed high ferritin levels (mean=6024 ng/ml). So, the higher level of ferritin, especially in the early phase, should be considered important and should lead the physician to another differential diagnosis including SoJIA.

In conclusion, systemic inflammation in KD and SoJIA may be caused by similar cytokines derangements. Recurring fever, late-onset and IVIG-resistant arthritis, and high ferritin levels in patients with KD should raise the possibility of SoJIA.

Acknowledgments

We would like to thank the parents of the patients for permission to publish the data.

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